Decreased Anterior Cingulate Volume in Combat-Related PTSD

Steven H. Woodward, Danny G. Kaloupek, Chris C. Streeter, Christelle Martinez, Marie Schaer, and Stephan Eliez

Background: *Neuroanatomical data point to functional relationships between the anterior cingulate cortex (ACC) and subcortical centers regulating fear, in particular, the amygdala. Functional brain imaging has disclosed divergent patterns of ACC activation in persons with posttraumatic stress disorder (PTSD). In addition, two preliminary structural imaging studies have found evidence of smaller ACC volume in PTSD. We explored associations between PTSD and ACC volume in a relatively large sample of adult combat veterans in which PTSD, lifetime alcohol abuse/dependence, and Vietnam versus Gulf War service were crossed.*

Methods: *Subjects were US military combat veterans of the Vietnam and Gulf Wars recruited from two metropolitan areas served by allied Department of Veterans Affairs PTSD treatment/research centers. Anterior cingulate cortex volume was analyzed as a function of grouping factors with and without adjustment for body size.*

Results: *Posttraumatic stress disorder was associated with smaller anterior cingulate cortex volume. This effect persisted in subjects without histories of alcoholism, did not interact with cohort effects, and was not modified by adjustment for body size.*

Conclusions: *Anterior cingulate cortex volume is substantially smaller in association with combat-related PTSD, a finding broadly consistent with cingulate hypofunctionality in that disorder.*

Key Words: Stress disorders, posttraumatic, magnetic resonance imaging, gyrus cinguli

Keen interest has emerged in the role that the anterior cingulate cortex (ACC) might play in posttraumatic stress disorder (PTSD) (Hamner et al 1999; Pitman et al 2001; Taber et al 2003; Villarreal and King 2001). Of particular interest are this region's close neuroanatomical relationships with subcortical components of the "central fear system," including the amygdala and locus coeruleus (Carmichael and Price 1995; Jodo and Aston-Jones 1997; Jodo et al 1998; McDonald et al 1996; Vogt et al 1979, 1987, 1995; Vogt and Pandya 1987). If the ACC supplies inhibitory regulation of the amygdala, then attenuation of that regulation could provide an avenue for understanding multiple features of PTSD. Absolute or relative hypoactivation of ACC during tasks involving exposure to traumatic reminders in persons with PTSD has now been replicated in three laboratories (Bremner et al 1999a, 1999b; Lanius et al 2001, 2003; Shin et al 1999, 2001). Accompanying such findings are indications that the ACC is coupled to the hypothalamic-pituitary-adrenal (HPA) axis. The cingulate cortex contains the largest concentration of receptors for corticotropin-releasing factor (CRF) among all cortical areas in the brain of the rhesus macaque (Sanchez et al 1999). As well, there have been observations of pyramidal cell apical dendritic remodeling in ACC following glucocorticoid challenge (Wellman 2001) and restraint stress (Radley et al 2004), similar to those originally motivating exploration of hippocampal volume in PTSD (Bremner et al 1995; Pitman et al 2001). Taken together, these findings suggest that reduced ACC volume might be found in association with PTSD.

Two preliminary structural magnetic resonance imaging (MRI) studies have made observations compatible with this hypothesis. Rauch et al (2003) reported smaller pregenual ACC and subcallosal cortex volumes (the latter combining portions of Brodmann's areas 32, 11, and 25) in nine Vietnam combat nurses with PTSD as compared with nine combat nurse control subjects. These authors did not find smaller dorsal ACC volume and invoked the preferential coupling of pregenual ACC and subgenual cortex to amygdala to explain this specificity. In their sample, ACC volume reductions were not associated with comorbid major depression. Using voxel-based morphometry, Yamasue et al (2003) found evidence of ACC gray matter hypodensity in 9 survivors of the Tokyo subway sarin attack with diagnoses of lifetime PTSD (1 also met criteria for current PTSD) as compared with 16 survivors who had never met criteria for PTSD. Here, we report on an effort to replicate these findings in a well-characterized sample of 99 survivors of combat and military operational stress. This sample also allowed us to account for variance associated with lifetime alcoholism and, to a limited degree, with normal aging.

Methods and Materials

Recruitment and Screening

Subjects provided written informed consent in accordance with procedures of the Institutional Review Boards of either Stanford University Medical School/VA Palo Alto Healthcare System or Boston VA Medical Center and the McLean Hospital. Subjects were recruited through a combination of advertising and word-of-mouth contacts with current and past patients and research volunteers. Initial screening established that subjects were US military veterans of the Vietnam Conflict or the Persian Gulf War (GW) who had been exposed to substantial military operational stress but now reported no current or past central nervous system (CNS) disease or psychosis and no alcohol or substance abuse/dependence in the last 6 months. Screening exclusions were based on low stress exposure, current alcohol or substance use, high fever(s), loss of consciousness requiring medical attention, or known contraindications to magnetic reso-

From the Clinical Laboratory and Education Division and Psychology Service (SHW), National Center for PTSD, VA Palo Alto Healthcare System, Palo Alto, California; Behavioral Science Division (DGK), National Center for PTSD, VA Boston Healthcare System, Division of Psychiatry (DGK, CCS), Boston University School of Medicine, Boston, Massachusetts; and Department of Psychiatry (CM, MS, SE), University of Geneva, Geneva, Switzerland.

Address reprint requests to Steven H. Woodward, Ph.D., National Center for PTSD, Clinical Laboratory and Education Division, Mail Code 334 PTSD, VA Palo Alto HCS, 3801 Miranda Avenue, Palo Alto, CA 94034; E-mail: steve.woodward@med.va.gov

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nance (MR) scanning. As a result of formal diagnosis, additional volunteers were excluded because they were negative for current military PTSD but positive for lifetime civilian PTSD (18), or were positive for current/recent alcohol/drug abuse (14), probable brain damage (6), or psychosis (2). In addition, four subjects later withdrew due to fatigue or nicotine withdrawal; two missed their scanning appointments and were unreachable; and five withdrew due to claustrophobia. After participating, 11 additional subjects were excluded due to imaging artifact and 2 due to previously undiagnosed brain injury. The final sample included 55 subjects from the Palo Alto site and 44 from the Boston site. Completing subjects were paid $200.

Final sample characteristics are presented in Table 1. The sample included 99 military veterans of either the Vietnam Conflict or the Gulf War. Subjects classified as PTSD-positive (PTSD+) met criteria for current PTSD as a result of experiencing one or more military traumas. Subjects classified as PTSD-negative (PTSD-) had also been exposed to military operational stress but were free of diagnosable PTSD, current or lifetime, due to military *or* civilian trauma. (All control subjects met DSM-IV PTSD Criterion A1, and all but three met Criterion A2). Alcohol abuse/dependence-positive (ETOH+) subjects were so classified based on meeting lifetime but not current alcohol abuse or dependence criteria (minimum period since meeting criteria: 6 months). Gulf War veterans had a mean age of 38 years, and Vietnam veterans had a mean age of 56 years.

Psychometrics

Subjects meeting screening criteria were administered both interview and self-report measures. Semistructured interviewing was conducted by trained and experienced Masters-level staff using the Clinician-Administered PTSD Scale (CAPS) (Blake et al 1997) for PTSD symptoms and selected Axis I modules of the Structured Clinical Interview for the DSM-IV (SCID) (First et al 1995) addressing mood episodes (e.g., major depression), psychotic and associated symptoms, alcohol and other substance use disorders, and anxiety and other disorders (e.g., panic disorder). Self-report instruments included the Combat Exposure Scale (CES) (Keane et al 1989), the Life Events Checklist (LEC) (Blake et al 2000), the Mississippi Scale for Combat-Related PTSD (MISS) (Keane et al 1988), the Beck Depression Inventory (BDI) (Beck et al 1961), and the Michigan Alcohol Screening Test-Short Form (SMAST) (Selzer 1971).

Brain Imaging

Magnetic resonance imaging was performed using two 1.5 T General Electric Signa scanners (GE, Fairfield, Connecticut) at similar hardware and software revisions, one at the Diagnostic Radiology Center of Veterans Affairs Palo Alto Healthcare System and one at the Brain Imaging Center of McLean Hospital (Belmont, Massachusetts). Coronal images were acquired with a three-dimensional (3-D) volumetric pulse sequence (repetition time [TR] = 35 milliseconds, echo time [TE] = 6 milliseconds, flip angle = 45°, number of excitations [NEX] = 1, matrix size = 256 × 192, field of view = 24 cm^2, slice thickness = 1.5–1.7 mm, 124 slices). Image optimization was performed in BrainImage (BrainImage 5.x, Stanford University, Stanford, California) following the standard protocols of the Stanford Psychiatry Neuroimaging Laboratory. Image optimizations included correction for inhomogeneity artifact, resampling to cubic (.9375 mm^3) voxels, positional normalization by reference to the anterior and posterior commissures and intrahemispheric fissure, skull-stripping, tissue segmentation based on a constrained fuzzy algorithm (Reiss et al 1998), and parcellation according to a modified Talairach grid (Kates et al 1999; Talairach and Tournoux 1988).

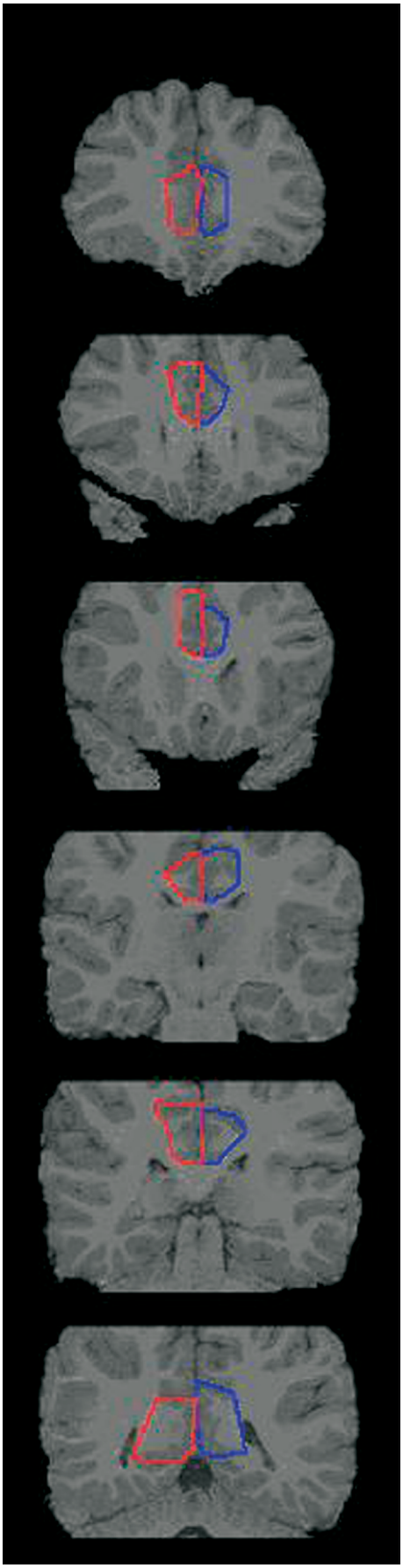
Manual delineation of the cingulate cortex followed a protocol developed by one of the authors (SE). Left and right cingulate gyri were first traced in sagittal view on slices 5 millimeters lateral to the midline. Next, a coronal view was used to draw the superior, inferior, lateral, and medial boundaries of the cingulate

Table 1. Subject Characteristics and Anterior Cingulate Cortex Volumes

	Vietnam Cohort		Persian Gulf Cohort					
	PTSD+	PTSD−	PTSD+	PTSD−	PTSD	COHORT	ETOH	Interactions
N	38	25	13	23				
Age	53.5 (2.6)	56.0 (3.5)	37.0 (5.7)	36.7 (3.9)	n.s.	$p < .001$	$p = .011$	PTSD × COHORT $p = .027$ PTSD × COHORT × ETOH $p = .001$
% Male	100	100	77	83	n.s.	$p < .001$	n.s.	n.s.
% Caucasian	65.8	92.0	53.8	69.6	$p = .041$	n.s.	$p = .041$	n.s.
% Current MDD	78.9	4.0	69.2	4.3	$p < .001$	$p = .037$	n.s.	n.s.
% Lifetime MDD	89.5	28.0	76.9	17.4	$p < .001$	$p = .012$	n.s.	n.s.
% Lifetime ETOH	44.7	44.0	46.2	39.1	n.s.	n.s.		n.s.
Age at ETOH + Onset	24.6 (8.0)	21.5 (8.7)	26.7 (5.0)	22.1 (5.9)	n.s.	n.s.		n.s.
Years of Education	14.4 (1.8)	15.5 (2.2)	14.3 (1.7)	15.0 (1.9)	$p = .016$	n.s.	n.s.	n.s.
Combat Exposure Scale	29.8 (9.9)	24.2 (8.2)	19.9 (11.8)	8.6 (6.0)	$p < .001$	$p < .001$	n.s.	COHORT × ETOH $p = .041$
BDI	25.0 (8.9)	4.6 (3.7)	21.0 (7.3)	4.3 (4.0)	$p < .001$	n.s.	n.s.	n.s.
SMAST	3.9 (4.0)	2.1 (3.8)	3.3 (3.6)	0.5 (.9)	$p < .001$	$p = .035$	$p < .001$	PTSD × ETOH $p = .012$
MISS	122.8 (18.8)	68.2 (15.8)	107.8 (15.8)	59.0 (11.1)	$p < .001$	$p = .001$	$p = .038$	n.s.
CAPS Total Severity	75.9 (18.4)	8.8 (9.0)	75.9 (19.9)	8.4 (11.0)	$p < .001$	n.s.	n.s.	n.s.
WAIS Vocabulary Score	47.4 (12.0)	55.5 (7.1)	45.6 (12.4)	52.5 (8.0)	$p < .001$	n.s.	n.s.	PTSD × ETOH $p = .032$
Left ACC Volume in mL	6.9 (1.7)	8.6 (1.7)	6.6 (2.0)	7.6 (1.9)	$p < .001$	n.s.	n.s.	n.s.
Right ACC Volume	7.9 (3.0)	8.9 (2.0)	8.3 (2.1)	9.4 (2.1)				

Tabulation of demographic, diagnostic, and psychometric data by PTSD diagnosis and COHORT. *p*-values of main effects associated with the grouping factors are indicated in columns headed PTSD, COHORT, and ETOH, respectively. Column headed Interactions lists any interactions.

PTSD, posttraumatic stress disorder; ETOH, alcohol abuse/dependence; MDD, major depressive disorder; BDI, Beck Depression Inventory; SMAST, Michigan Alcohol Screening Test-Short Form; MISS, Mississippi Scale for Combat-Related PTSD; CAPS, Clinician-Administered PTSD Scale; WAIS, Wechsler Adult Intelligence Scale; ACC, anterior cingulate cortex; n.s., not significant.



cortex and adjacent white matter (see Figure 1). These boundaries were defined medially by the interhemispheric cortical surface and laterally by a line connecting the deepest extension of the cingulate sulcus to the deepest extent of cingulate gray matter ribbon directly superior to the corpus callosum (CC). The region of interest excluded tissue subjacent to the genu of the CC and posterior to a line dropped from the apex of the genu. Excessive intersubject variability in landmarks precluded delineation of subgenual cingulate cortex.) Posterior to the division of the splenium of the CC, the inferior border of the cingulate was defined by the calcarine fissure. Lastly, a dynamic Talairach grid was fitted on each brain (see Figure 2). In the rostrocaudal direction on a coronal anterior commissure-posterior commissure (AC-PC) oriented stack, Talairach sectors corresponding to B, C, D, and E1 in Figure 2 defined the anterior portion of the cingulate, while sectors E2, E3, F, G, and H defined the posterior portion. Two of the authors (C.M. and M.S.) performed all manual tracing of the cingulate blind to subject identity and diagnosis. Intraclass correlation coefficients of .94 calculated over two independent raters indicated good interrater reliability for cingulate volume measurements.

Statistics

Primary analyses involved repeated-measures analysis of variance (ANOVA) with three grouping factors (PTSD, ETOH, COHORT) and two within factors (anterior versus posterior and right versus left). Follow-up analyses considered Talairach ACC subvolumes B through E1. Analyses of unadjusted volumes were repeated with adjustment for cerebral tissue volume, cranial volume, or Wechsler Adult Intelligence Scale (WAIS) vocabulary. Selected analyses were restricted to nonalcoholic subjects. Posttraumatic stress disorder effect sizes were estimated via "pooled d+" (Hedges and Olkin 1985) to accommodate unequal numbers of GW and Vietnam cohort members across the four PTSD by ETOH subgroupings. Finally, correlational analyses were conducted on ACC volumes and selected continuous PTSD severity measures to assess parametric covariations.

Results

The ACC was larger in the right hemisphere while the posterior cingulate cortex (PCC) was larger on the left [interaction of hemisphere and anterior-posterior dimension: $F(1,91) = 25.6$, $p < .001$]. There was no main effect of hemisphere and no interaction between hemisphere and any grouping factor. The ACC [$F(1,91) = 11.7$, $p = .001$] but not the PCC [$F(1,91) = .056$, n.s.] was smaller in subjects diagnosed with PTSD [interaction of PTSD and anterior-posterior factor: $F(1,91) = 5.28$, $p = .024$; see Figure 3). The effect of PTSD on ACC volume did not interact with ETOH or with COHORT (all Fs < 1). Neither ETOH nor COHORT was associated with a main effect on ACC volume (all Fs < 1). No effect or interaction involving PTSD, ETOH, or COHORT on ACC volume was substantially modified by adjusting for cranial volume, cerebral tissue volume, or WAIS vocabulary. Likewise, the exclusion of seven female subjects had no impact on the results.

When repeated in ETOH- subjects, the effect of PTSD on total ACC volume persisted [$F(1,51) = 6.77$, $p = .012$]. Posttraumatic stress disorder effect sizes across the ETOH+ and ETOH- subsamples were comparable (ETOH+: d+ = −.71, 95% confi-

Figure 1. Successive coronal slices indicating manual tracings of cingulate cortical tissue areas on a typical brain.

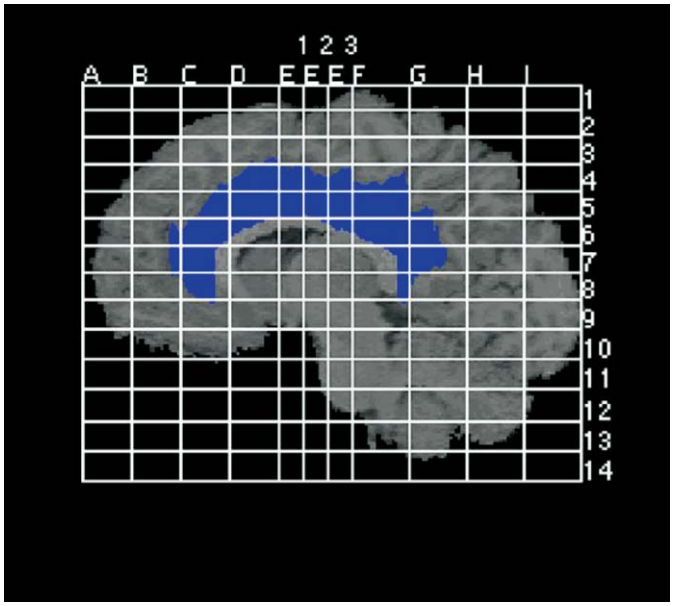


Figure 2. Sagittal view of the cingulate region of interest (ROI) of a typical brain upon which has been superimposed a Talairach grid in accordance with standard locators.

dence interval [CI] = −1.34 to −.09; ETOH-: d+ = −.78, 95% CI = −1.35 to −.21).

A second repeated-measures ANOVA was performed in which the within factors represented a finer parcellation of the ACC (two hemispheres by four Talairach ACC subvolumes B though E1). This analysis did not find a significant interaction of PTSD and subvolume [$F(3,89) = 2.67$, $p_{H\text{-}F} = .053$; $\varepsilon = .714$], though there was a trend toward a slightly larger effect at the B subvolume roughly corresponding to pregenual ACC (see Figure 4).

When computed across all subjects, a pattern of inverse correlations was evident between continuous measures of PTSD severity and ACC volume (CAPS total severity score: rho[97] = −.332, $p < .001$; MISS: rho[96] = −.339, $p < .001$); however, the correlation between ACC volume and BDI only approached significance (rho[95] = −.197, $p < .053$).

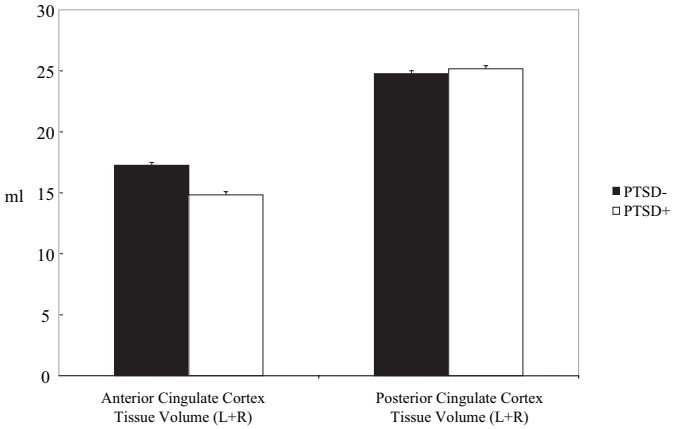


Figure 3. Comparison of PTSD effects at anterior and posterior cingulate cortices. PTSD, posttraumatic stress disorder; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex.

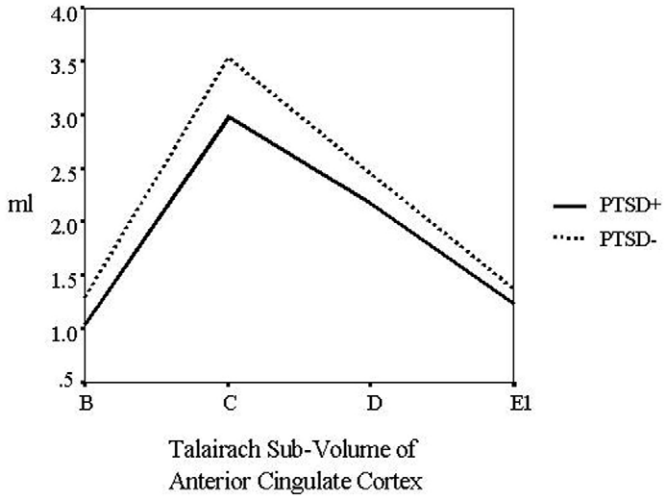


Figure 4. Comparison of PTSD effects at Talairach subvolumes B–E1 of anterior cingulate cortex. PTSD, posttraumatic stress disorder.

Discussion

This analysis of 99 combat veterans confirmed and extended previous findings. Anterior cingulate cortex volume was observed to be smaller in persons with combat-related PTSD whether or not they were diagnosed with lifetime alcoholism or belonged to one of two military/aging cohorts. Statistical adjustment for body size did not modify the results. We did not find that the effect of PTSD was limited to pregenual ACC. Our data suggested instead that dorsal ACC, often associated with more cognitive functions (Bush et al 2000), is also reduced in volume in PTSD. We did not assess subcallosal cortical volume and therefore we could not replicate this aspect of the observations of Rauch et al (2003).

To our knowledge, ACC volume has not been specifically considered in prior studies of the effects of alcoholism on the brain. The absence of a COHORT effect on ACC volume is compatible with two studies that failed to find normative aging effects on this structure (Jernigan et al 1991; Raz et al 1997). Acknowledging that the cohorts did not differ greatly in age, this absence is interesting in light of the exaggerated vulnerability to aging exhibited by nearby dorsolateral frontal cortex (Raz et al 1998, 2004).

The findings of this study are compatible with data suggesting the ACC is hypofunctional in PTSD. In addition to those studies noted in the introduction, functional imaging studies in normal humans using both MR and positron emission tomography (PET) have shown that the ACC is activated by tasks requiring behavioral monitoring/inhibition (Kerns et al 2004; Menon et al 2001) and emotion regulation (Ochsner et al 2002), both domains relevant to the clinical symptomatology of PTSD. Of special interest, Hariri et al (2003) found evidence of ACC involvement in the downregulation of amygdala reponses to generic threat cues in normal subjects. The directionalities of all these results are compatible with the observed terminations of cortical afferents on inhibitory interneurons within the amygdala (Carmichael and Price 1995; McDonald et al 1996). Notwithstanding the appeal of a simple ACC hypoactivation model, *hyperactivation* of ACC in PTSD subjects during the generation of trauma-related images has also been reported (Lanius et al 2004; Rauch et al 1996; Shin et al 1997). Both Zubieta et al (1999) and Liberzon et al (1999) observed ACC hyperactivation in PTSD patients during exposure

to trauma-related sounds. Anterior cingulate cortex hyperactivation has also been observed during script-driven dissociation (Lanius et al 2002). Relatedly, Gilboa et al (2004) performed an analysis of interregional cerebral blood flow (CBF) correlations during script-driven imagery and found correlations between amygdala and ACC metabolism to be *positive*. As more studies become available, some of these inconsistencies may be resolved by consideration of differences among anterior cingulate subregions (Bush et al 2000; Vogt et al 1992), between tasks, or between the measurements employed. Until then, we should consider the full complement of functional interactions between anterior cingulate and amygdala to be potentially relevant to PTSD.

The effort to understand the contribution of ACC to PTSD can capitalize on a rich cognitive electrophysiological literature focusing on this region. Anterior cingulate cortex gives rise to multiple scalp-recordable electrophysiological events, including the error-related and feedback negativities (Herrmann et al 2004; Holroyd et al 1998; Mathalon et al 2003; Miltner et al 2003) and midline frontal theta (Asada et al 1999; Gevins et al 1997; Ishii et al 1999). These phenomena have already exhibited associations with anxiety (Aftanas and Golocheikine 2001; Hajcak et al 2003; Inanaga 1998). Their examination in PTSD is now strongly warranted.

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